The effect of cannabis on tremor in patients with multiple sclerosis

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Abstract—Background: Disabling tremor is common in patients with multiple sclerosis (MS). Data from animal model experiments and subjective and small objective studies involving patients suggest that cannabis may be an effective treatment for tremor associated with MS. To our knowledge, there are no published double-blind randomized controlled trials of cannabis as a treatment for tremor in MS patients. Methods: The authors conducted a randomized double-blind placebo-controlled crossover trial to examine the effect of oral cannador (cannabis extract) on 14 patients with MS with upper limb tremors. There were eight women and six men, with a mean age of 45 years and mean Expanded Disability Status Scale score of 6.25. Patients were randomly assigned to receive each treatment and the doses escalated over a 2-week period before each assessment. The primary outcome was change on a tremor index, measured using a validated tremor rating scale. The study was powered to detect a functionally significant 50% improvement in the tremor index. Secondary outcomes included accelerometry, an ataxia scale, spiral drawing, finger tapping, and nine-hole pegboard test performance. Results: Analysis of the data showed no significant improvement in any of the objective measures of upper limb tremor with cannabis extract compared to placebo. Finger tapping was faster on placebo compared to cannabis extract (p < 0.02). However, there was a nonsignificant trend for patients to experience more subjective relief from their tremors while on cannabis extract compared to placebo. Conclusions: Cannabis extract does not produce a functionally significant improvement in MS-associated tremor.

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Tremor is a rhythmic, involuntary oscillatory movement of a body part and was detected in 58% of 100 randomly selected multiple sclerosis (MS) patients attending a hospital clinic. Tremor in MS characteristically occurs on action and produces disability in about 27% and incapacity in about 10% of cases. It typically affects the upper limbs, although it may involve the legs, head, and trunk. The presence of tremor in MS is associated with an increased frequency of wheelchair dependence and a worse Expanded Disability Status Scale score (EDSS). The severity of MS tremor correlates with the severity of dysmetria, dysarthria, and dysdiadochokinesia, suggesting that it arises from involvement of the cerebellum or its connections.

MS tremor tends to respond poorly to medication, including clonazepam, hyoscine, isoniazid, glutethimide, carbamazepine, primidone, and ondansetron. Although propranolol (160 to 320 mg) is often used it has not been shown to be effective in MS. Stereotactic surgery, targeting the thalamus (ventralis intermedius or ventralis oralis posterior), zona incerta, or the subthalamic nucleus can produce marked improvement in contralateral upper limb tremor and manual function in highly selected cases. It is not known whether deep brain stimulation is preferable to lesional surgery, although a randomized study (with five patients in each arm) comparing the two techniques showed similar outcomes. However, both techniques are associated with significant morbidity.

Up to 8% of patients with MS use cannabis and anecdotal reports suggest that there may be some beneficial effect on pain, nausea, muscle spasms, bladder symptoms, and tremor. However, little formal quantitative work investigating the effects of cannabis on MS patients has been performed. In a survey of 112 MS patients utilizing cannabis, tremor relief was one of the most commonly reported benefits of the drug; 90% of tremulous patients (making up 43% of the sample) reported an improvement in their tremor after taking cannabis. Furthermore, more than 50% of these patients felt that their tremor was “much better.”

Randomized-controlled trials assessing the effect of cannabis on MS tremor are scarce. Clifford performed a single-blind study in which 5 to 15 mg of delta-9-tetrahydrocannabinol (THC), one of the main active components of cannabis, or placebo was administered to eight patients who had MS-associated tremor. Tremor scores improved significantly on cannabis compared to placebo. However, the study was limited due to lack of blinding. Further studies are needed to determine the efficacy and safety of cannabis for treating tremor in MS.
tremor and ataxia. Their tremor was assessed before and after treatment. Six of these patients reported no effect with THC but two experienced significant tremor reduction and some functional improvement, for example in writing and eating, although no formal quantification of these effects was undertaken. In addition, there is one report in which an MS patient experienced a considerable reduction of his action tremor after smoking marijuana. His view was supported by objective evidence as improvement in ataxia was noted on clinical ratings and electromyographic recordings showed that his 3 Hz tremor was virtually abolished, whereas it had caused a 1 to 3 cm displacement of the fingers.

The effect of cannabis on animal models of MS has also been studied: both THC and the cannabinoid receptor agonist WIN55,212 were successful in reducing both spasticity and tremor, measured with a strain gauge and by accelerometry, in CREA (chronic relapsing experimental allergic encephalomyelitis) mice. Additionally, some mice without tremor became tremulous after injection of a CB1 receptor antagonist. Although studies are underway assessing the effectiveness of cannabinoids for specific problems such as spasticity and bladder symptoms in MS, these will not deal with MS-related tremor.

Consequently, in view of the evidence suggesting that cannabis might have a role in the treatment of MS tremor, we endeavored to investigate this in more detail with a randomized controlled crossover trial.

Methods. Ethical approval for this study was obtained from the Plymouth Local Research Ethics Committee. Signed informed consent was obtained from each patient prior to enrollment in the study according to the Declaration of Helsinki. The study was performed at the Peninsula Medical School, Plymouth, between May 3 and 31, 2002. The flow of patients through the trial is summarized in the CONSORT diagram in figure 1.

Entry criteria were diagnosis of definite MS (Poser criteria), age between 18 and 64 years, and a visible upper limb tremor. Patients were excluded if they had cognitive impairment rendering them unable to give informed consent, had a history of ischemic heart disease or psychotic illness, or were unwilling to stop driving for the period of the study. Participants. Fourteen patients with definite MS and a visible upper limb tremor were recruited from the neurology clinics of Derriford Hospital, Plymouth, and the Royal Cornwall Hospital, Truro. Twenty-seven patients were initially asked to take part; 13 of these declined or were found to be unsuitable for the study. Baseline history, examination, Kurtzke EDSS, and Barthel index were obtained from each participant prior to entry into the study.

Interventions. The study used a randomized controlled double-blind crossover design with three assessments at 2-weekly intervals. Patients were randomly assigned to receive orally either active treatment for the first 2 weeks followed by placebo for the second 2 weeks or vice versa. The medication used was cannabidiol, an ethanol extract of cannabis sativa standardized to 2.5 mg of THC per capsule, or an identical placebo capsule. Cannabidiol was provided by the Society for Oncological and Immunological Research in Berlin. As cannabinoids are variably absorbed from the gut, the study incorporated a dose titration phase in which the dose was escalated at 3-day intervals until either the patient reached a maximum of 0.125 mg/kg of THC per day or they began to experience intolerable side effects, in which case the dose was dropped to the last tolerated dose. The treating physician (P.F.) contacted the patients every third day by telephone to advise about dose. This dose titration took place over the 2 weeks between each assessment, with the patient reaching a stable dose for a minimum of 4 days prior to each assessment (figure 2).

At each visit, the following measurements were performed while the patients were seated comfortably:

1. The severity of tremor using a previously validated 0 to 10 clinical rating scale. The severity of postural tremor (scored while the arm was held outstretched [P1] and then in the basking [P2] position) and intention tremor (I) (scored during the finger to nose to finger test) were scored individually from 0 to 10 in each arm and the total score (0 to 60) taken as a Tremor Index (TI).

2. Tremor visible in two drawings of a spiral. The spiral drawings were anonymized and the order randomized before being graded by a blinded rater on a 0 to 10 scale. The mean of the two scores was used.

3. The mean number of pegs inserted per second from two performances of a timed standard 9-hole pegboard test.

4. The number of taps/10 seconds on a calculator key. This task was performed twice and the mean value taken.

5. The severity of arm ataxia in each arm was scored on a (0 to 4) clinical ataxia scale.

6. Frequency (Hz) and magnitude (mV) of the principle peak in spectra obtained while the arm was held outstretched using

Figure 1. CONSORT flow diagram.

Figure 2. The visit schedule and dose escalation protocol. C = clinic visit, T = telephone consultation.
an EGAX-5/12M/6M miniature accelerometer attached with tape to the dorsum of the hand, between the second and third metacarpal, using a technique previously described.12

Accelerometry was repeated three times at each visit and the mean frequency and amplitude values taken.

7. A standardized video recording of the patients’ postural and intention tremor was also made.

For spirometry, the 9-hole pegboard test, the tapping task, and accelerometry measurements were obtained from the same (worst affected) arm throughout the study.

We assessed whether orally administered THC produced a functionally significant (50%) reduction in upper limb tremor in patients with MS compared to placebo treatment. The primary outcome was a reduction in the TI. The results of spirometry, pegboard test, tapping task, accelerometry, and ataxia scale were secondary outcomes. Power calculations based on data obtained from a previous study estimated that with a sample size of 14 there was a 90% chance of detecting a 50% reduction in tremor with THC compared to placebo.13 A random sequence was generated using an Excel spreadsheet. This sequence was used by the pharmacy in conjunction with the patient’s trial number to dispense cannabis and then placebo or vice versa. To prevent unmasking due to the presence of known side effects, two blinded assessors (P.G.B. and S.G.) carried out the assessments, while a separate treating physician (F.P.) monitored the patients’ progress. The patients and assessors were also separately asked at each assessment whether THC or placebo had been administered. Possible answers were active, placebo, or unsure.

Statistical methods. For both primary and secondary outcomes the trial data were analyzed as a simple two-period crossover trial. A two-sample t-test was applied to period 1 — period 2 differences for the two groups of patients, those in the cannabidase placebo group versus those in the placebo-cannabidase group. The difference between the means of the two groups was taken as twice the size of the treatment effect.

Results. Fourteen patients entered the study. Eight were women and six were men, with a mean age of 45 years (range: 35 to 56), mean EDSS of 6.25 (range: 3.5 to 7.5), and mean Barthel score of 13.2 (range: 4 to 20). One patient admitted to previous cannabis use. One woman (Case 12) dropped out after completing the baseline and active treatment assessments because of a family emergency. Thus statistical analysis was performed on the data obtained from the remaining 13 cases.

The doses reached by each patient are shown in table 1. Overall, patients reached a mean dose of 0.107 mg/kg (range 0.042 to 0.125 mg/kg) twice a day of THC on active treatment, and a dose equivalent to 0.123 mg/kg (range 0.094 to 0.125 mg/kg) twice a day when on placebo. Five patients considered their tremors to have improved on cannabis extract compared to only one on placebo (Fisher exact test p = 0.08). All the patients had bilateral upper limb action tremors with postural and intention components; rest tremor was not encountered. The mean (± SD) baseline scores for the TI are shown in table 2. The size of any effect of treatment on the TI for each individual was close to zero (0.45) and there was no difference between the two groups (p = 0.55) (see supplementary figure E-1 at www.neurology.org).

The mean (± SD) baseline scores for the secondary outcomes are shown in table 2. There was no significant improvement in the spiral scores, accelerometry results, functional tests (tapping and pegboard tasks), or ataxia scale on cannabis extract compared to placebo (see table 2). However, the rate of finger tapping appeared significantly worse on cannabis extract than placebo (table 3).

Nine of the 14 patients correctly identified which drug

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<th>Patient number</th>
<th>Target dose by weight (mg THC bid)</th>
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bid = twice a day.

ey they were on. However, the assessors felt unable to guess the medication used in any of the cases.

Adverse events were mild. Ten patients reported adverse symptoms while on cannabis extract and two while on placebo. Adverse symptoms most commonly reported while on cannabis extract were drowsiness and lightheadedness; memory disturbance, dysphoria, euphoria, increased appetite, and dry mouth were also described.

Discussion. We sought to refute or confirm data obtained from previous anecdotal reports that had suggested that cannabis alleviated tremor associated with MS.8–10 We found that orally administered cannabis extract had no significant positive impact on upper limb tremor index or any of the other objective evaluations (pegboard test, spiral drawings, ataxia ratings, and accelerometry) in 14 tremulous MS patients. However, there was a nonsignificant trend for patients to report improvement in their tremor, with five patients noting improved tremor on cannabis extract compared to only one on placebo.

The one effect reaching significance was an apparent slowing of finger tapping on cannabis extract compared to placebo. However, closer examination of the data (see table 3) reveals that this was largely the result of improved scores on placebo compared to baseline, rather than a worsening of scores on cannabis extract relative to baseline. Nevertheless, it is possible that cannabis extract blocked a learning effect that had allowed scores to improve with practice while patients were on placebo.

The difference between the subjective and objective results obtained in this study may have been chance, as the trend for patients to report subjective tremor improvement with cannabis extract was not significant. However, alternative explanations include that the mood enhancing or cognitive effects of

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cannabis caused patients to feel less troubled by their tremors, even though they were objectively unchanged. This would account for the large number of patients reporting improvement of tremor with cannabis in previous questionnaire-based studies. We consider the monitoring of both subjective and objective improvements to be critical in assessing effectiveness when using potentially mood-altering medication. Second, it may reflect unblinding of some of the patients, although not the assessors, in the current trial as a result of cannabis’s side effects, which may have led to some bias in self-reported symptoms. Third, it is possible that cannabis extract did not improve upper limb tremor magnitude or function, which we measured, but conceivably may have improved tremor magnitude elsewhere in the body, an internal feeling of tremulousness (internal tremor), or tremor occurrence rate (the duration for which tremor is present per day), which we did not assess. Finally, a small improvement in tremor, below that which this study was powered to detect, may have nonetheless been perceived by patients.

The side effects experienced by our patients while on cannabis extract were generally mild, as has been found in previous trials involving people with MS. Furthermore, our trial design, with upward dose titration until side effects appeared or maximum dose by weight was achieved, helped to ensure that severe side effects did not occur. This design also explains why most (10/14) patients experienced at least some side effects while on active treatment.

It is of interest that two previous studies have noted beneficial effects of cannabinoids on objectively measured MS tremors or on functional performance. Several reasons for these discrepancies with our results are possible: first, that other studies were not conducted according to a double blind randomized placebo-controlled protocol and thus may reflect bias; second, that the cannabis extract used here (cannador) did not contain a tremorlytic substance present in the cannabis preparations used in other studies; third, that inhalation is necessary for an antitremor effect, as reported in one case, although this would not explain the positive findings in two of eight cases in the study performed by Clifford; fourth, that a subgroup of patients with MS tremor, with as yet unidentified characteristics, may benefit from cannabis, although the patients in our study had action tremors typical of those seen in MS; and finally, that doses of cannabis used in our study may not have reached a critical threshold to alleviate MS tremor.

It remains possible that cannabis causes a subjective effect on tremor, perhaps mediated through its influence on mood or mental function, or a small objective effect below which this study was powered to detect. While this might raise the possibility of using cannabis in a palliative setting, it seems unlikely that it has an important role in the functional relief of tremor in patients with MS.

Acknowledgment

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References